IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

ROCHE PALO ALTO LLC, GILEAD PALO ALTO, INC. and GILEAD SCIENCES, INC., Plaintiffs, v. LUPIN PHARMACEUTICALS, INC. and LUPIN LTD., Defendants.	Civ. A. No. 2:10-03561 (EJS) (SCM) *DOCUMENT FILED ELECTRONICALLY*

LUPIN'S CLAIM CONSTRUCTION SUBMISSION REGARDING CONSTRUCTION OF PLASMA LEVEL CLAIM TERMS

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The plasma level claim language (Trial Tr. vol. 10, 136:2-7) requires achieving the claimed plasma levels in individual patients, and not as means or averages of a group of patients.

I. Legal standards.

The claim construction analysis considers (1) the ordinary meaning; (2) whether the specification justifies departing from the ordinary meaning; and (3) whether the prosecution history compels an alternative meaning. (*See, e.g.,* Claim Construction Op. 2-5, ECF No. 121).

II. Lupin's proposed claim construction is the ordinary meaning: the claimed plasma levels refer to plasma levels measured in individual patients.

Several Asserted Claims contain elements directed to maintaining ***ranolazine plasma levels*** in a, or the, human patient. (*See* Exh. A). Experts for both sides admit the claim language "a" human patient or "the" human patient refers to treating an individual patient. (Trial Tr. vol. 4, 84:13-22, 88:9-89:5 (Zusman); Trial Tr. vol. 3, 44:19-45:8 (Weiner) ("Q. You interpret that as a single human patient? A. When you treat, you treat individuals, of course.")). Here, the ordinary meaning of "ranolazine plasma levels" in a, or the, human patient thus is naturally understood as requiring achieving the claimed plasma levels in individual patients. *See, e.g., Nautilus Neurosciences, Inc. v. Wockhardt USA LLC*, Nos. 11-1997 (ES), 12-1243 (ES), 2013 WL 775750, at *6-7 (D.N.J. Feb 27, 2013) ("Means for enhancing said average T_{max}" construed as referring to "a human patient" not "in more than one human patient"); *Acorda Therapeutics Inc. v. Apotex Inc.*, No. 07-4937 (GEB-MCA), 2011 WL 4074116, at *4 (D.N.J. Sept. 6, 2011) (plasma level claim term referred to the blood plasma of an individual, not a group average).

III. The '057, '328 and '258 claims that contain plasma level elements (*e.g.,* "ranolazine plasma levels in the human patient of about 550 to 7500 ng base/mL") should not be construed to require mean plasma level measurements.

A. Plaintiffs have not demonstrated a lexicography definition applies to the actual language appearing in the claims.

Plaintiffs argue the ordinary meaning of patient plasma levels is inapplicable since the specification provides what Plaintiffs characterize as a lexicography definition directed to mean values. (4/24/13 Mots. Tr. 30:9-17; Trial Tr. vol. 2, 113:11-114:4, 115:6-119:1 (Weiner)). But Plaintiffs' so-called "lexicography" text referring to mean values does so when defining a plasma ranolazine ***concentration***, not the claimed plasma ranolazine ***level***:

> Plasma ranolazine concentration is a mean concentration determined by analyzing the concentration of ranolazine in as few as five to as many as ten humans who are on the same dosing schedule. It is important that the ranolazine concentration is a mean value because of variances in ranolazine concentrations in individuals that may be caused by differences in weight, metabolism, or disease states which may cause one person to metabolize ranolazine faster or slower than an average person. The plasma ranolazine levels are determined from drawn blood onto heparin.

(*See, e.g.,* DTX12A-0004, '057 Patent, col. 3 ll. 27-36). Since the Asserted Claims lack the phrase "plasma ranolazine concentration," and instead recite "plasma ranolazine level" or "plasma ranolazine levels", the above specification text is a definition inapplicable to the claims.

B. Plasma concentrations and plasma levels are not synonymous precisely because the latter pertains to individuals.

The specifications of the Asserted Patents counsel against equating a plasma concentration with a plasma level. The last sentence in the "lexicography" paragraph above Plaintiffs rely on distinguishes a plasma ranolazine *concentration* from plasma ranolazine *levels*, the latter of which the specification confirms originates from "drawn blood onto heparin." (*Id.*) Plaintiffs' expert Dr. Weiner admitted that this test result only comes from an individual patient:

> Q. Now, the last sentence, we didn't focus on this Friday, but it says the plasma levels ranolazine levels are determined from drawn blood on to heparin. Do you see that?
> A. Yes.
> Q. Would you agree when you draw blood to measure plasma you do that one patient at a time?
> A. Yes.
> Q. You get a single concentration for a single plasma level for a single patient?
> A. Yes.

(Trial Tr. vol. 3, 49:17-50:2 (Weiner)).

Likewise, the various specification Examples Plaintiffs repeatedly parroted to support their mean-not-individual theory used the phrase plasma *concentration* when referring to averaged values or expressly used the term "mean".[1] Thus, even if it were assumed that the phrase plasma ranolazine *concentration* deserved a lexicography definition, since that phrase is not found in the claims, it does not control the claim construction of plasma ranolazine *levels*. *See Merck & Co. v. Teva Pharm. USA Inc.*, 395 F.3d 1364, 1370 (Fed. Cir. 2005) (holding patentee must clearly express intent to act as lexicographer, and lexicography must appear with "reasonable clarity, deliberateness, and precision"); *Acumed LLC v. Stryker Corp.*, 483 F.3d 800, 807 (Fed. Cir. 2007) (two similar terms used in the same specification are evidence the patentee considered them to have distinctly different meanings).

C. The surrounding claim language in the claims does not compel treating patients to assess mean values.

The claim language itself also does not compel imposing a non-ordinary "average value" construction on the plasma ranolazine level elements. There is no dispute the person of ordinary skill understands that a mean or averaged value is accompanied by a ± range or other expression of standard deviation from the mean. (Trial Tr. vol. 2, 69:8-17, 116:12-117:11 (Weiner); vol. 4, 39:6-40:24, 41:22-42:13, 44:25-46:1, 49:1-24 (Mayersohn); *id.* at 87:22-88:8 (Zusman)). No

[1] *See, e.g.,* DTX12A-0007, '057 Patent, col. 10 ll. 1-6 (Example 3, "mean peak plasma *concentration*" and "mean trough plasma *concentrations*"); *id.* at -0008 col. 12 ll. 20, 40 (Example 4, same); *id.* at -0009, col. 13 ll. 28-29 (Example 4, "The plasma mean peak concentrations ranged from 1346 to 2128 ng per mL…"); *id.*, col 13. l. 36 (same); *id.* at -0010, tbl.6 (Example 6, discussing "mean" pharmacokinetic parameters); *id.*, col. 15 ll. 54-64, *id.* at -0011, col. 16 ll. 6-23 (in Examples 6 and 7, expressly using "mean" values of concentration; peak plasma levels of 4-6 or 2-4 hours are inconsistent with mean values reported for T_{max}); *id.*, col. 16 ll. 29-38 (Example 8, reporting that both "individual and mean concentrations" were measured); *id.*, col. 17 l. 9 (Example 8, describing "mean plasma profiles"); *see also* Trial Tr. vol. 3, 49:1-52:12 (all of Dr. Weiner's examples from the specification referred to mean *concentrations*); Trial Tr. vol. 4, 48:3-22 (Mayersohn); *id.* at 150:1-151:5, 151:25-153:6, 155:13-156:5, 159:22-161:2 (Zusman)).

such ± values or standard deviation measure appears in the claims. (DTX12A-0011, '057 Patent, col. 18 ll. 23-27; DTX16A-0013, '328 Patent, col. 19 ll. 29-35, col. 20 ll. 28-34; DTX22A-0012, '258 Patent, col. 18 ll. 40-49). The claims also do not set forth selection criteria or method steps relating to identifying the patients to fit into any 5-10 person "average" measurements.[2] Thus, neither the plain meaning of the claims nor their structure compels a focus on patient averages.

D. Plaintiffs ignore the context of the *Wyeth* case and its limited specification.

Plaintiffs repeatedly suggested *Wyeth v. Lupin Ltd.*, 579 F. Supp. 2d 711, 718-19 (D. Md. 2008) supports their position. There, the court concluded that the claim language "to a patient" normally signals individual patients are involved. *Id.* at 719 & n.7. For the claim requirement directed to blood plasma levels of "no more than about 150 ng/mL," the parties agreed that this could be an individual measurement. *Id.* at 719. When the district court separately evaluated *times* to peak blood plasma levels, however, it rightly invoked an average value because the *sole* support for the hour ranges found in the claims was based on time-to-T_{max} values, and "[t]he specification does not present evidence of T_{max} values of individual patients." *Id.* at 719. This lack of written description support, and ambiguity based on inability to achieve such average values, also served as the basis for Lupin's § 112 challenge to the Wyeth patents. *Id.* at 722-23.

If Plaintiffs want to apply the *Wyeth* decision, and stipulate they have no individual patient data to support their claimed ratios in the specification or their provisional patent application (*see generally* DX3), then this Court can by all means similarly proceed to invalidate the claims under § 112 for indefiniteness (because who qualifies as an "average" patient or which patients are to include in the "averaging" process is left unstated) and lack of written

[2] Indeed, if Plaintiffs insist that this process of identifying a group of 5-10 patients and averaging patient outcomes is an implicit requirement of what it has claimed, then there is not and will never be any infringement by Lupin's ANDA products, since the undisputed evidence of record is that this type of "group therapy" will not occur. (Trial Tr. vol. 4, 84:13-85:9, 88:18-89:5 (Zusman); Trial Tr. vol. 3, 44:23-45:17 (Weiner)).

description support (if, as Plaintiffs contend, there is no evidence in the specification of individual patients achieving these claimed ranges). However, in fairness to the specification, and unlike in *Wyeth*, Lupin acknowledges that specific numerical blood plasma levels that appear in the claims do appear elsewhere in the Abstract and specification, in the context of statements applicable to individual patients, such as (bold emphasis added):

- "The formulation is . . . useful . . . to maintain human plasma ranolazine levels at between 550 and 7500 ng base/mL," (DTX12A-0002, '057 Patent, Abstract);
- "This invention involves…methods for administering sustained release ranolazine dosage forms of this invention to provide for therapeutic plasma levels of ranolazine," (*id.* at -0004, col. 3 ll. 55-58);
- "The method includes administering . . . ***to the human patient*** to maintain ranolazine plasma levels in the human patient of from about 550 to about 7500 ng base/mL for at least 24 hours . . . ," (*id.* at -0003, col. 2 ll. 19-24; *see also id.*, col. 2 ll. 30-36 (same, but limiting ranolazine plasma levels to a 1000 to 3900 ng base/mL range); *id.* at -0010, col. 16 ll. 24-26 ("useful ranolazine plasma levels can be achieved in humans with dosing of this SR formulation on a bid schedule"));
- "The [SR] formulations of this invention are administered one, twice [sic]; or three times in a 24 hour period in order to maintain a plasma ranolazine level above the threshold therapeutic level and below the maximally tolerated levels, of between about 550 and 7500 ng base/mL ***in a patient***," (*id.* at -0006, col. 7 ll. 19-24);
- "The peak plasma ranolazine levels are typically achieved at from about 30 minutes to eight hours or more after initially ingesting the dosage form . . . . It is preferred that the [SR] dosage forms of this invention are administered in a manner that allows for a peak ranolazine level no more than 8 times greater than the trough . . . ," (*id.*, col. 7 ll. 48-55).

Thus, quite unlike the specification in *Wyeth*, the specifications here expressly evaluates plasma levels (particularly for the numerical ranges found in the claims) in the, or a, human patient, *i.e.,* on an individual level. Lupin's position here does not conflict with the reasoning in *Wyeth*; nor does *Wyeth* compel construing plasma levels here as averages.

IV. Conclusion.

Lupin thus respectfully requests that the Court construe the claims' plasma level-related claim language as requiring achieving the claimed plasma levels in individual patients.

Respectfully submitted,

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